Short Communication

Molecular Epidemiology of HIV-1 in Afghanistan, Iran, and Pakistan

Fatemeh Jahanbakhsh[1], Sana Eybpoosh[2], Ehsan Mostafavi[2], Ali Akbar Haghdoost[3], Kayhan Azadmanesh[1*]

[1]Virology Research Group, Pasteur Institute of Iran, Tehran, Iran;
[2]Department of Epidemiology and Biostatistics, Research Centre for Emerging and Reemerging Infectious Diseases, Pasteur Institute of Iran, Tehran, Iran;
[3]HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran.

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We conducted this study to obtain a comprehensive picture of molecular epidemiology of HIV-1 in three neighboring countries, *i.e.* Afghanistan, Iran, and Pakistan as a basis for discussing possible hypothesis regarding between-country virus transmission. Our results showed that subtype composition differs between these countries with more variation in Pakistan than Iran and Afghanistan. The CRF35-AD clade was predominant in Afghanistan and Iran while the A1 subtype was predominant in Pakistan. HIV-1 sequences obtained from Pakistan (belonging either to B, A1, or CRF35_AD clades) did not group with the sequences obtained from Afghanistan and Iran. However, CRF35_AD clades from Afghanistan made two significant clusters with those strains from Iran. The results also showed that CRF35_AD clades from Afghanistan had more diversity than those in Iran suggesting its older presence in this country. Putting these findings together and considering drug trafficking/immigration events from Afghanistan to Iran we hypothesized that HIV epidemics might have been transmitted from Iran to Afghanistan. However, the reverse order might also be true but with less support from the existing evidence. There was no indication of Iran-Pakistan HIV transmission. Performing sophisticated evolutionary analysis is needed to test these hypotheses about the origin and transmission pattern of the virus among these countries. *J Med Microbiol Infec Dis, 2015, 3 (3-4): 44-47*.

Keywords: Molecular Epidemiology, HIV-I, Afghanistan, Iran, Pakistan.

By the aid of social and molecular epidemiological studies, our knowledge about the HIV epidemic in the Middle East and North African (MENA) countries has improved in the recent years. In this regard, Mumtaz *et al.* (2014) have conducted a comprehensive review of the state of the HIV epidemic in 23 countries of the region. Using the information of the reviewed citations, they also have discussed the within-country and between-country patterns of HIV transmission. For example, they have reported that the HIV epidemic in People Who Inject Drugs (PWIDs) is started in Iran and moved from there to Afghanistan and Pakistan [1]. Although the review provides valuable information about the state of HIV epidemic in the region, the claim mentioned above about HIV transmission from Iran to Afghanistan and Pakistan persuaded us to assess if molecular and social data within these three neighboring countries is enough and supportive of this claim or not. After providing a clearer picture of the molecular epidemiology of HIV in these countries, especially among PWIDs, we discussed this claim as well as alternative hypotheses that can be derived from the origin and transmission pattern of the virus based on available data.

First, we conducted a systematic literature review on all peer-reviewed published papers in PubMed database (until May 2014) addressing molecular epidemiology of HIV-1 (14 studies) in Afghanistan (n=3) [2-4], Iran (n=8) [5-12], and Pakistan (n=3) [13-15]. We also searched HIV Sequence Database at the Los Alamos National Laboratory (LANL) for sequences registered from these countries. A phylogenetic analysis was then conducted on partial (*gag*, *pr*, *rt* and *env regions*) and full genome sequences of subtypes/recombinant forms commonly circulating among these countries (*i.e.* subtype B and CRF35_AD). In this regard, multiple sequence alignment was performed using MUSCLE program, and genetic distances were calculated based on the maximum composite likelihood model using MEGA software (v6.0).

Our findings showed that, Iran has the highest number of HIV-1 registered sequences in the GenBank (total=1067, number for PWIDs=228) comparing to Pakistan (total=708, number for PWIDs=362) and Afghanistan (total=26, number for PWIDs=10). Figure 1 shows subtype composition of the HIV population in these countries, regardless of their risk group.

***Correspondence:** Kayhan Azadmanesh
Department of Virology, Pasteur Institute of Iran, No. 69, Pasteur Ave, Tehran, Iran, 1316943551.
Email: k.azadmanesh@gmail.com

Tel/ Fax: +98 (21) 66496682

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In Afghanistan, the only circulating clade among PWIDs was CRF35_AD. CRF35_AD was also predominant among PWIDs of Iran; however, subtype B and CRF01_AE were also seen in a few cases of this risk group. Although CRF35_AD was also seen in Pakistan, it has not been detected among PWIDs and is not the predominant clade there at all. In this country, the predominant clade either in general population or among PWIDS was subtype A1. Other clades that were observed among PWIDs in Pakistan included CRF01_AE and A1G.

Results of the phylogenetic analysis showed that although CRF35_AD strains circulating among PWIDs of Iran and Afghanistan clustered together significantly, there were at least two main clusters of Iranian-Afghan PWIDs. Previously, this finding had been reported by Jahanbakhsh *et al.* (2013) [6]. Moreover, analysis of within-subtype variation on amino acid sequence data showed that after adjustment for '*sampling year'* the diversity of CRF35_AD isolates in Afghanistan is higher than Iran.

Putting these findings together, some issues come to the mind that worth discussion. In case Iran was the source of the epidemic among PWIDs in Pakistan and Afghanistan, we expect to see the same strains circulating at list among PWIDs of these countries. However, the subtype distribution seems to be different either in general population (Fig. 1) or among PWIDs of these countries. This applies in particular in the case of Iran and Pakistan because no common HIV clades have been reported among Iranian and Pakistani PWIDs. Also, subtype B sequences that have been reported in Pakistan (n=44) with unknown risk group did not make a cluster with Iranian B subtypes. These findings undermine the hypothesis that Iran is the source of HIV epidemic in Pakistan.

Although the B subtype which was not seen in Afghanistan was quite common among Iranian PWIDs, subtype distribution among PWIDs of Afghanistan and Iran is considered to be similar with the CRF35_AD being the predominant clade in both countries. This finding suggests that the virus might have been transmitted between PWIDs of Afghanistan and Iran. Mumtaz *et al.* (2014) [1] suggested that the HIV has transmitted unidirectionally from Iran to Afghanistan, through the infection of Afghan refugees during their migration to Iran. Although this might be true, the reverse scenario might also be the case. The *reverse hypothesis* especially seems logical because CRF35_AD sequences in Afghanistan are of more diversity than those of Iran, which can be suggestive of the older presence of the virus in Afghanistan. If the *reverse hypothesis* was true, then, HIV-1 CRF35_AD clade might have been transmitted to Iran through drug trafficking routes or by migration of Afghan refugees to Iran during 1980s - 1990s. It should be noted that Iran has been identified as the major route of drug trafficking from Afghanistan, the largest opium producing country in 2010, to Europe [16]. Moreover, Iran has been the world's second major recipient of Afghan refugees experiencing at least three waves of Afghan migration since the 1850s [17]. By December 2013, more than 800,000 Afghan refugees have been lived in Iran most of whom arrived before 2001 (till 1 January 2001, 1,482,000 Afghan refugees arrived Iran [17, 18]. Illegal and transitory movement of Afghan people to Iran is also an ongoing event which provides the opportunity for the virus to circulate among Afghanistan and Iran permanently and makes it hard to elucidate the origin of HIV epidemic in these countries (Fig. 2).

Mumtaz *et al.* (2014) have supported their claim by pointing to similarities of viral subtypes in these countries and citing two descriptive studies on molecular epidemiology of HIV-1 in Afghanistan (2007) [2] and Iran (2009) [9] and one systematic review (2011) of molecular epidemiological studies on HIV-1 in the MENA region [19], which also included the two above citations [1].

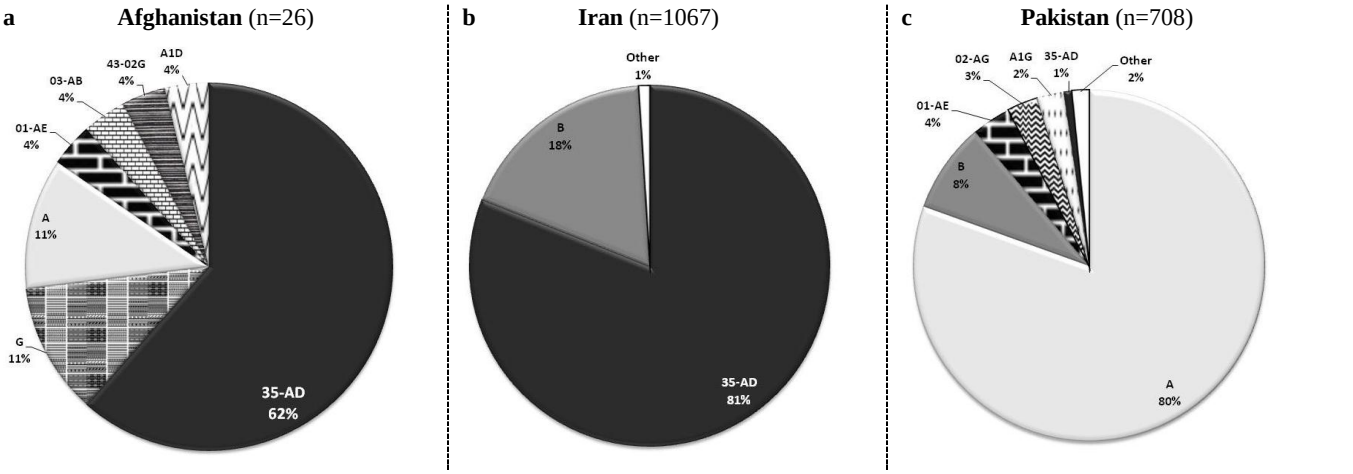


Fig. 1. HIV-1 subtype composition among general HIV population (regardless of risk group) in Afghanistan (a), Iran (b) and Pakistan (c). Even with a few number of samples obtained from Afghanistan (n=26), this country shows the highest diversity in subtype composition. While Iran has largest number of registered sequences, it shows the lowest diversity.

Numbers in the pie chart are proportions (%) of each subtype to the total number of identified subtypes in each country. Retrieved from Los Alamos National Laboratory (LANL) from http://www.hiv.lanl.gov/content/index

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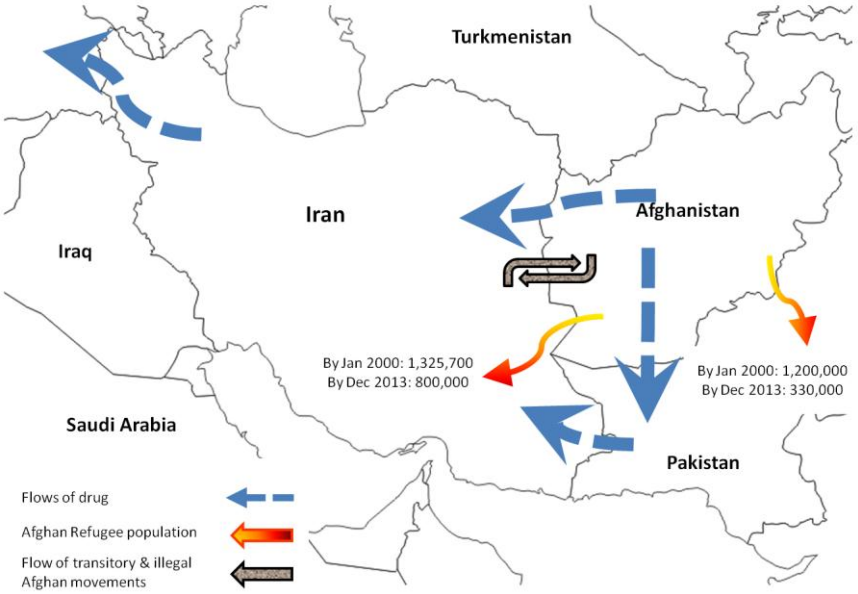


Fig. 2. Drug trafficking routs between Afghanistan, Iran, and Pakistan and estimated number of Afghan refugees in Iran and Pakistan. Data retrieved from United Nations Office on Drug and Crime (UNODC) [20] and United Nations High Commissioner for Refugees (UNHCR) [17, 18, 21]

We would like to note that even if the molecular epidemiology of an epidemic in a region is well-known, making conclusive statements about the origin and transmission pattern of the virus in that region is prone to bias if we only rely on such information. Descriptive studies on molecular epidemiological data, when combined with socio-demographic information, can only help us to generate "hypothesis" about the origin and transmission pattern of the virus. Such hypothesis should then be tested using further evolutionary analyses on molecular data. The authors of this review, however, have not performed evolutionary analyses to test their hypothesis. Also, it seems that the molecular epidemiology of HIV in these countries has not been comprehensively regarded while deriving this conclusion by Mumtaz and his colleagues [1].

As a conclusion, we have to note that based on available data and our phylogenetic and distance analyses, it is not possible to go beyond "hypotheses" at this stage and derive "causal" inferences about the origin and transmission pattern of HIV-1 among Afghanistan, Iran, and Pakistan. In this regard, observing two distinct HIV-1 CRF35_AD clusters containing both Iranian and Afghan PWIDs, besides the ongoing movement of Afghans across national borders of Iran and Afghanistan further complicates the hypothesis generation about the transmission pattern of the epidemic across Afghanistan and Iran. Availability of a complete HIV-1 genome sequences from these countries will provide the opportunity to elucidate the origin and transmission pattern of the HIV-1 epidemic in the region through sophisticated evolutionary analyses.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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